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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/664,519	09/18/2000	Michael C. Barney	660005.98757	4670

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EXAMINER	
KAM, CHIH MIN	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 01/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/664,519	BARNEY ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-8,12,14,15,17-23 and 25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-7,12,14,15,17-21 and 25* is/are rejected.

7)☒ Claim(s) *8 and 22* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The Request for Continued Examination (RCE) filed November 25, 2003 under 37 CFR 1.114 is acknowledged. An action on the RCE follows.

Status of the Claims

2. Claims 1, 3-8, 12, 14, 15, 17-23 and 25 are pending.

Applicants' amendment and Declaration of inventor, Michael C, Barney filed November 25, 2003 are acknowledged, and Applicants' response has been fully considered. Claims 1, 12, 15 and 23 have been amended, and claims 2, 13, 16 and 24 have been cancelled. Thus, claims 1, 3-8, 12, 14, 15, 17-23 and 25 are examined.

Rejection Withdrawn

Claim Rejections - 35 USC § 112

3. The previous rejection of claim 16 under 35 U.S.C.112, second paragraph, is withdrawn in view of applicant's cancellation of the claim in the amendment filed November 25, 2003.

Claim Rejections - 35 USC § 103(a)

4. The previous rejection of claim 2 under 35 U.S.C. 103(a) as being unpatentable over Nutter *et al.* (WO 98/11883) in view of Todd *et al.* (U. S. Patent 5,082,975), is withdrawn in view of applicant's cancellation of the claim in the amendment filed November 25, 2003.

5. The previous rejection of claims 13, 16 and 24 under 35 U.S.C. 103(a) as being unpatentable over Nutter *et al.* (WO 98/11883) in view of Todd *et al.* (U. S. Patent 5,082,975) as applied to claim 1, further in view of Lefren *et al.* (U. S. Patent 4,431,427), is withdrawn in view of applicant's cancellation of the claim in the amendment filed November 25, 2003.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1, 6 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nutter *et al.* (WO 98/11883) in view of Todd *et al.* (U. S. Patent 5,082,975).

Nutter *et al.* teach a method of killing cancer cells or bacterial cells, and/or inhibiting their growth through the use of beta acids (also known as lupulones) such as hexahydrocolupulone (HHC) (page 4, line 12-page 5, line 10), and a pharmaceutical composition comprising the beta acid and a pharmaceutical carrier (page 9, lines 14-22; claim 6), which can be used as a topical ointment for topical administration (page 9, lines 23-25; page 10, line 27-page 11, line 17; claim 7) to inhibit the growth of Staphylococcus Aureus (page 6, line 27-page 7, line 6). The reference indicates lupulones can be administered in a dosage from 0.5 mg to 100 mg/kg (page 11, lines 26-30), which corresponds to 0.5 - 100 ppm (0.5 mg/kg = $0.5 \times 10^{-3}/1000$

g/g = 0.5 ppm; claim 1). However, the reference does not indicate HHC at 0.2-25 ppm would not prevent the growth of lactobacilli. Todd *et al.* (U. S. Patent 5,082,975) shows HHC at high concentration (50-200 ppm, column 7, lines 54-58) inhibits the growth of certain lactobacilli. Therefore, if the concentration of HHC is reduced to a lower concentration such as in the range of 0.2-25 ppm, the inhibition of the growth of lactobacilli would be lessened, thus allow the growth of lactobacilli. At the time of invention was made, it would have been obvious to one of ordinary skill in the art that HHC at lower concentration such as 0.2-25 ppm would inhibit the growth of S. aureus without preventing the growth of lactobacilli as indicated by Nutter *et al.* and Todd *et al.* Thus, the combined references result in the claimed invention and were, as a whole, prima facie obvious at the time the claimed invention was made.

In response, applicants indicate Todd *et al.* teach lactobacillus is killed at concentration level above 50 ppm, however, the reference does not teach the HHC concentration levels below 50 ppm would lessen the inhibitory effect of HHC on lactobacilli, e.g., the reference does not report any experiments conducted at concentrations below 50 ppm and provides no guidance as to whether and at what concentrations below 50 ppm HHC will stop inhibiting lactobacilli growth and prolifiration; and Table 1 (right column, pH 5.0) of the instant application indicates there is no growth of S. aureus when testing hexahydro beta acid at concentrations of 50, 100 or 0.2-25 ppm, thus, lowering the concentration does not automatically lessen the inhibitory action, which demonstrates the unpredictability of antibacterial action. Therefore, Todd *et al.* do not provide the conclusion that HHC concentration at 0.2-25 ppm lessened the inhibitory effect of HHC on lactobacilli; and Declaration of invenor Michael C. Barney further provides evidence of the unpredictability of antibacterial action, which states without the benefit of experimentations

reported in the instant application, it would have been impossible to predict the effects of a lower concentration of HHC (such as 0.2-25 ppm) on the growth of lactobacilli, especially at the vaginal pH of 4.5-5.0 on the growth of lactobacilli (pages 7-10 of the response). The response has been fully considered, however, the argument is not found persuasive because of the following reasons: the data in Table 1 (right column, pH 5.0) are directed to S. aureus, not to lactobacilli as indicated in Todd *et al.*, and the data of Table 1 do not demonstrate the unpredicatbility of antibacterial action since some growth of S. aureus is indicated under the conditions of pH 6.0 and 7.0 and at 0.2-1.56 ppm of hop acid (left and middle columns), and the MIC assay for lactobacillus is also performed at pH 6.3 (Table 2), thus, lowering the concentration of hop acid does lessen the inhibitory action of the bacteria as indicated at pH 6.0 or 7.0; although Todd *et al.* do not indicate the inhibition level of lactobacilli growth at 0.2-25 ppm of HHC, it is obvious that the inhibition of lactobacilli growth would be lessened if the concentration of HHC is reduced by 250 fold (50/0.2); and Nutter et al. teach a method of killing bacteria such as S. aureus using the amount of HHC having the same range cited in the claimed method, thus, it would be expected that HHC at concentration 0.2-25 ppm would inhibit the growth of S. aureus without preventing the growth of lactobacilli.

In the Declaration of Michael C. Barney, Paragraph one states he is the first named inventor of the instant application; Paragraph two states he has read examiner's comments in the advisory action dated October 16, 2003 regarding Todd *et al.* reference; Paragraph three states without the benefit of experimentation reported in the instant application, it would have been impossible to predict the effects of a lower concentration of HHC (such as 0.2-25 ppm) on the growth of lactobacilli; Paragraph four indicates Hop acids such as HHC inhibit the growth of

bacteria by disrupting ion transport across bacterial cell membranes, however, it is difficult to predict the number of the molecules needed to disrupt ion transport across particular bacterial cell membranes; Paragraph 5 indicates Todd et al. show HHC inhibits the growth of certain lactobacilli in milk (pH 6.4-6.8) at 50-200 ppm, however, these experiments cannot be used to predict the minimum number of molecules needed to disrupt ion transport across lactobacilli bacterial cell membranes, particularly at the vaginal pH 4.5-5.0; Paragraph 6 indicates the activity of hexahydro beta acid at 50 and 100 ppm does not provide the prediction of the activity at 0.2 to 25 ppm, see Table 1 (right column, pH 5.0) of the instant application, which indicates there is no growth of S. aureus when testing hexahydro beta acid at concentrations of 50, 100 or 0.2-25 ppm, thus, lowering the concentration does not automatically lessen the inhibitory action; Paragraph 7 indicates the summary states the response of all organisms to hop acids is unpredictable as all organisms are different, thus, the activity of hop acids on lactobacilli below 50 ppm level at vaginal pH 4.5-5.0 cannot not be predicted from Todd *et al.* The Declaration of Michael C. Barney has been considered, however, it is not found persuasive because the data in Table 1 indicates the inhibitory action of hop acid against S. aureus at pH 6.0 or 7.0 is concentration dependent, e.g., there is no growth of S. aureus at 100 and 50 ppm, but some growth of the bacteria is found at 0.2-1.56 ppm of hop acid, thus the inhibition of lactobacilli growth (at pH 6.4-6.8) would be lessened if the concentration of HHC is reduced by 250 fold (50/0.2). It appears that the data in Table 1 and the comments in the Declaration indicate the inhibitory action of hop acid against bacteria is pH dependent, however, this limitation is not indicated in the claim. Furthermore, Nutter et al. teach a method of killing bacteria such as S. aureus using the amount of HHC which is in the same range of hop acid indicated in the claimed

invention. Therefore, it would be expected that HHC at concentration 0.2-25 ppm would inhibit the growth of S. aureus without preventing the growth of lactobacilli.

7. Claims 3-5, 12, 14, 15, 17-21, 23 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nutter *et al.* (WO 98/11883) in view of Todd *et al.* (U. S. Patent 5,082,975) as applied to claim 1 above (and to more accurately state the rejection, claims 1, 6 and 7), further in view of Lefren *et al.* (U. S. Patent 4,431,427).

Nutter *et al.* teach a method of killing cancer cells or bacterial cells, and/or inhibiting their growth through the use of beta acids (also known as lupulones) such as hexahydrocolupulone (HHC) (page 4, line 12-page 5, line 10), and lupulones can be administered in a dosage from 0.5 mg to 100 mg/kg (page 11, lines 26-30), which corresponds to 0.5 - 100 ppm (0.5 mg/kg = 0.5 x 10^{-3}/1000 g/g = 0.5 ppm). Todd *et al.* (U. S. Patent 5,082,975) shows HHC at high concentration (50-200 ppm, column 7, lines 54-58) inhibits the growth of certain lactobacilli. The combined references teach HHC at a low concentration such as in the range of 0.2-25 ppm would inhibit the growth of lactobacilli without prevent the growth of lactobacilli (claim 1). However, Nutter *et al.* and Todd *et al.* do not disclose the use of a product comprising an absorbent and HHC. Lefren *et al.* teach a tampon containing an organic acid in the absorbent material such as cotton fibers to create a hostile but safe environment during the use of tampon to inhibit the growth of pathogenic bacteria such as S. aureus and the compounds should be in an amount to maintain the fluids in the tampon at a pH of 4.5-2.5 (column 1). Therefore, at the time the invention was made, it would have been obvious to a person of ordinary skill in the art to use a product such as tampon as taught by Lefren *et al.* but substituting the organic acid with HHC in the absorbent material at concentration of 0.2-25 ppm (claims 3-5,

12, 14) to inhibit S. aureus without preventing the growth of lactobacilli to maintain normal bacterial flora in a use environment such as vaginal area to avoid the onset of other bacterial infections (claims 15, 17-21, 23 and 25). Thus, the combined references result in the claimed invention and were, as a whole, prima facie obvious at the time the claimed invention was made.

In response, applicant indicates the data for S. aureus inhibition by hexahydro beta acids demonstrate the unpredictability of antibacterial action, thus the amended claims are in no way obvious over Nutter et al., Todd et al., or Lefren et al. taken alone or in combination (see pages 7-10 of the response). The argument is not found persuasive because Lefren *et al.* teach using a tampon containing an organic acid in the absorbent material to create a hostile but safe environment to inhibit the growth of pathogenic bacteria such as S. aureus and the proper acidic pH should be maintained in the tampon, and Nutter et al., Todd et al. teach HHC at a low concentration such as in the range of 0.2-25 ppm would inhibit the growth of lactobacilli without prevent the growth of lactobacilli, thus the combined references of Nutter *et al.*, Todd *et al.* and Lefren *et al.* teach the use of tampon containing HHC for affecting the growth of S. aureus in the vaginal area as indicated in the section above.

8. Claims 8 and 22 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

9. Claims 1, 3-7, 12, 14-15, 17-21, 23 and 25 are rejected, and claims 8 and 22 are objected to.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (703) 308-9437. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D. CMK
Patent Examiner

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December 22, 2003

CHRISTOPHER S. F. LOW
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